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Clustering of other metabolic risk factors in subjects with metabolic syndrome

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Abstract

Various anthropometric indices have been proposed for metabolic syndrome. We investigated the clustering of metabolic risk factors other than components of metabolic syndrome and physical activity in subjects with and without metabolic syndrome as defined by different anthropometric indices. The subjects comprised 6141 men and 2137 women who underwent routine health examinations in Tokyo. We compared metabolic risk factors (high low-density lipoprotein cholesterol, hyperuricemia, high γ-glutamyltransferase, fatty liver) and sedentary history in subjects with and without metabolic syndrome as defined by the American Heart Association by substituting various proposed anthropometric indices of abdominal obesity (waist circumference ≥85, ≥90, or ≥102 cm for men and ≥90, ≥80, or ≥88 cm for women; waist-to-height ratio ≥0.5 for both men and women). Irrespective of the anthropometric index or sex, the age-adjusted odds ratios for risk factors and sedentary history were all significantly greater in subjects with metabolic syndrome (men and women: 1.26∼1.35 and 2.06∼2.63 for high low-density lipoprotein cholesterol, 2.36∼2.60 and 3.88∼7.20 for hyperuricemia, 2.54∼3.02 and 2.92∼4.05 for high γ-glutamyltransferase, 4.42∼4.87 and 9.43∼12.27 for fatty liver, and 1.37∼1.50 and 1.43∼1.72 for sedentary history). Findings still persisted in those not receiving medication for diabetes mellitus or coronary heart disease. Therefore, attention should be paid to other metabolic risk factors in subjects with metabolic syndrome, irrespective of the anthropometric index or sex. Further study is also needed to clarify the most appropriate definition of metabolic syndrome so as to include the spectrum of risk factors that best represents the future risk of cardiovascular and other diseases.

1. Introduction

The Adult Treatment Panel III created a definition for metabolic syndrome in 2001, highlighting the study and management of this syndrome [1]. In 2005, the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) issued a scientific statement after a minor revision of this definition [2]. The International Diabetes Federation (IDF) also issued a definition for metabolic syndrome in 2005 [3]; the waist circumferences (Ws) for the definition of abdominal obesity for Japanese were the same as those in the definition of the Japan Society for the Study of Obesity (JASSO) based on visceral fat area [4]. In 2006, IDF recommended that Japanese use the Asian values that are the same as the values for Asian Americans recommended by AHA/NHBLI [2,5]. However, the components for metabolic risk factors defined in metabolic syndrome are limited to cardiovascular risk factors; and the definition of abdominal obesity (W) differs by sex, by ethnic population, and even by country.

Although body mass index (BMI) is a widely used obesity index, most Asians are not prominently obese. Moreover, BMI does not always accurately indicate the degree of obesity [6]; and an increasing number of studies suggest that the degree of central fat distribution may be more closely related to metabolic risks than BMI [7,8]. In addition, BMI is difficult to calculate. Therefore, AHA/NLHBI, IDF, and JASSO have adopted the index of abdominal obesity, rather

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than BMI, in their criteria for defining metabolic syndrome. There is increasing evidence that the waist-to-height ratio (WHtR) may be a better anthropometric predictor for metabolic risks, atherosclerotic heart disease, and chronic renal disease [9-22]. We have reported that nearly all overweight Japanese men and women had WHtR of at least 0.5. This index is also more closely related to metabolic risks, especially in nonobese people, than other anthropometric indices [23-26].

Because metabolic syndrome may involve more risk factors than those included in its present definition and obesity indices for metabolic syndrome differ, the presence of other coexistent metabolic risks in subjects with metabolic syndrome as determined by various indices of abdominal obesity requires further exploration. On the other hand, physical inactivity may augment abdominal obesity and metabolic risks [1,27]. We are interested in studying both the broader range of metabolic syndrome and the possibility of incorporating various anthropometric indices of central fat distribution to cover a broader range of metabolic risks. Therefore, we compared the clustering of other metabolic risk factors and sedentary history between subjects with and without metabolic syndrome as defined by AHA/NHLBI [2] by substituting various proposed anthropometric indices of abdominal obesity, including WHtR, in both men and women.

2. Subjects and methods

2.1. Study population

The Japanese government encourages periodic health examinations for the early diagnosis of disease. Corporate employees often receive financial support from employers for such examinations. Millions of Japanese people have undergone such examinations in recent years. The subjects in this study were 6141 men (49.5 ± 8.9 years old [mean ± SD]; BMI, 14.7-37.5 kg/m^2) and 2137 women (51.9 ± 9.0 years old; BMI, 13.9-43.3 kg/m^2) who underwent health evaluations at a medical center in Tokyo [24].

2.2. Procedure and measurement

Height and weight were measured after an overnight fast. Waist circumference was measured at the umbilical level with the subjects standing and breathing normally [24]. Blood pressure was measured with the subjects in a sitting position. Plasma glucose, serum triglyceride, cholesterol, high-density lipoprotein (HDL) cholesterol, uric acid, and γ-glutamyltransferase were measured by enzymatic methods. Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald equation, but excluding the subjects with serum triglyceride of 400 mg/dL or greater [28]. Abdominal ultrasonography was performed during the same morning. At the option of the individual subjects, 6061 men and 2073 women received this examination. The current histories of all subjects receiving medication with respect to metabolic risk were investigated.

2.3. Definitions of obesity-related anthropometric risk factors, metabolic risk components of metabolic syndrome, and risk factors other than components of metabolic syndrome and sedentary history

2.3.1. Obesity-related anthropometric risk factors

1. Men: W at least 85 cm (JASSO) [4], at least 90 cm (AHA/NHLBI for Asian Americans) [2], or at least 102 cm (AHA/NHLBI for non–Asian Americans) [2].
2. Women: W at least 90 cm (JASSO) [4], at least 80 cm (AHA/NHLBI for Asian Americans) [2], or at least 88 cm (AHA/NHLBI for non–Asian Americans) [2].
3. Both men and women: WHtR at least 0.5 (our proposal) [24].

2.3.2. Metabolic risk components of metabolic syndrome (according to the criteria of AHA/NHLBI) [2])

1. Hypertension: systolic blood pressure at least 130 mm Hg and/or diastolic blood pressure at least 85 mm Hg and/or currently receiving medication for hypertension.
2. Hyperglycemia: fasting plasma glucose at least 100 mg/dL and/or currently receiving medication for hyperglycemia.
3. Hypertriglyceridemia: serum triglyceride at least 150 mg/dL and/or currently receiving medication for hypertriglyceridemia.
4. Low HDL cholesterol: serum HDL cholesterol less than 40 mg/dL for men and less than 50 mg/dL for women.

2.3.3. Metabolic syndrome

Presence of 3 or more risk factors from the above 5 risk factors (hypertension, hyperglycemia, hypertriglyceridemia, low HDL cholesterol, and the defined obesity-related anthropometric risk factor).

2.3.4. Other metabolic risk factors

1. High LDL cholesterol: serum LDL cholesterol of at least 140 mg/dL and/or currently receiving medication for hypercholesterolemia [29].
2. Hyperuricemia: serum uric acid greater than 7 mg/dL and/or currently receiving medication for hyperuricemia.
3. High γ-glutamyltransferase: serum γ-glutamyltransferase greater than 109 IU/L.
4. Fatty liver: bright liver, increased liver echotexture compared with kidneys, vascular blurring, and deep attenuation as shown by ultrasonography [30].

2.3.5. Sedentary history

Lack of regular exercise comprising at least 30 minutes per session at least once per week [27].

2.4. Statistics

Age, prevalence of metabolic risk factors other than components of metabolic syndrome, and sedentary history were compared in subjects with and without metabolic syndrome by substituting various anthropometric indices for the definition of metabolic syndrome using the t test and χ^2 test. The age-adjusted odds ratios for other metabolic risk factors and sedentary history in subjects with metabolic syndrome when substituting an anthropometric index for the definition of metabolic syndrome were compared by logistic regression, using subjects without metabolic syndrome as a reference group. JMP software (SAS Institute, Cary, NC) was used for analysis.

3. Results

3.1. Clinical features and the prevalence of other metabolic risk factors and sedentary history in men with and without metabolic syndrome when substituting an anthropometric index for the definition of metabolic syndrome

The number of subjects with metabolic syndrome varied according to which definition of anthropometric index was used, the largest being WHtR at least 0.5 (n = 1843) and the smallest being W at least 102 cm (n = 846) (Table 1). The age of the group with metabolic syndrome was significantly higher than that of the group without metabolic syndrome, irrespective of the anthropometric index used for the definition. The prevalences of other metabolic risk factors and of sedentary history were all significantly greater in those with metabolic syndrome than those without metabolic syndrome in men, irrespective of the anthropometric index used for the definition. At the time of the study, 69 subjects (1.12%) were currently receiving medication for diabetes; and 61 subjects (0.99%) were currently receiving medication for coronary heart disease.

3.2. Prevalence of other metabolic risk factors and sedentary history in women with and without metabolic syndrome when substituting an anthropometric index for the definition of metabolic syndrome

The number of subjects with metabolic syndrome also varied according to which anthropometric index was used in the definition, the largest being WHtR at least 0.5 (n = 287) and the smallest being W at least 90 cm (n = 140) (Table 2). The age of the group with metabolic syndrome was significantly higher than that of the group without metabolic syndrome irrespective of the anthropometric index used for the definition. The prevalences of other metabolic risk factors were all significantly greater in those with metabolic syndrome than in those without metabolic syndrome, irrespective of the anthropometric index used for the definition, whereas the prevalence of sedentary history was only significantly greater in women with metabolic syndrome defined by W at least 88 cm. At the time of the study, 10 subjects (0.47%) were currently receiving medication for diabetes; and 10 subjects (0.47%) were currently receiving medication for coronary heart disease.

3.3. Age-adjusted odds ratios of other metabolic risk factors and sedentary history in men with and without metabolic syndrome when substituting an anthropometric index for the definition of metabolic syndrome

In men, the age-adjusted odds ratios of other metabolic risk factors and sedentary history were all significantly higher in those with metabolic syndrome than in those without metabolic syndrome, irrespective of the anthropometric index used for the definition, even excluding those

Table 1
Clinical features and the prevalence of other metabolic risk factors and sedentary history in men with and without metabolic syndrome when substituting an anthropometric index for the definition of metabolic syndrome

Anthropometric index	JASSO [4]		AHA/NHLBI for Asian Americans [2]		AHA/NHLBI for non–Asian Americans [2]		Our proposal [24]	
	W ≥85 cm		W ≥90 cm		W ≥102 cm		WHtR ≥0.5	
Metabolic syndrome	No	Yes	No	Yes	No	Yes	No	Yes
n	4328	1813	4784	1357	5295	846	4298	1843
Age (y, mean ± SD)	49.2 ± 9.0	50.5 ± 8.5†	49.2 ± 9.0	50.3 ± 8.4†	49.3 ± 9.0	50.4 ± 8.5*	48.9 ± 8.9	50.9 ± 8.6†
High LDL cholesterol[a]	30.2%	36.2%†	30.4%	37.3%†	31.2%	36.8%*	29.9%	36.7%†
Hyperuricemia	15.1%	30.2%†	16.0%	32.1%†	17.4%	32.9%†	14.9%	30.4%†
High γ-glutamyltransferase	9.2%	21.7%†	9.9%	22.4%†	11.1%	23.9%†	8.9%	22.2%†
Fatty liver[b]	22.2%	55.0%†	23.9%	60.0%†	27.1%	61.8%†	21.9%	55.3%†
Sedentary history	68.0%	74.0%†	68.1%	75.6%†	69.0%	74.7%*	68.0%	73.9%†

Sixty-nine subjects (1.12%) were currently receiving medication for diabetes, and 61 subjects (0.99%) were currently receiving medication for coronary heart disease.

[a] A total of 6058 men (serum triglyceride <400 mg/dL) were included in the study of this item, which was calculated using the Friedewald equation.

[b] A total of 6061 men underwent this examination at the option of the individual subjects.

* $P < .05$.

† $P < .0001$.

Table 2
Clinical features and the prevalence of other metabolic risk factors and sedentary history in women with and without metabolic syndrome when substituting an anthropometric index for the definition of metabolic syndrome

Anthropometric index	JASSO [4]		AHA/NHLBI for Asian Americans [2]		AHA/NHLBI for non–Asian Americans [2]		Our proposal [24]	
	W ≥90 cm		W ≥80 cm		W ≥88 cm		WHtR ≥0.5	
Metabolic syndrome	No	Yes	No	Yes	No	Yes	No	Yes
n	1997	140	1885	252	1976	161	1850	287
Age (y, mean ± SD)	51.6 ± 9.0	55.9 ± 8.6†	51.4 ± 8.9	55.9 ± 8.7†	51.6 ± 9.0	55.6 ± 8.6†	51.3 ± 8.9	56.0 ± 8.5†
High LDL cholesterol[a]	35.6%	62.6%†	34.5%	58.4%†	35.2%	63.1%†	34.0%	59.2%†
Hyperuricemia	0.6%	5.0%*	0.6%	3.2%*	0.6%	4.4%*	0.6%	2.8%*
High γ-glutamyltransferase	1.9%	5.7%*	1.6%	5.6%*	1.7%	6.8%*	1.7%	4.9%*
Fatty liver[b]	10.0%	59.3%†	8.3%	50.8%†	9.6%	58.8%†	8.0%	47.6%†
Sedentary history	68.5%	75.7%	68.4%	73.4%	68.3%	77.0%*	68.3%	73.2%

Ten subjects (0.47%) were currently receiving medication for diabetes, and 10 subjects (0.47%) were currently receiving medication for coronary heart disease.

[a] A total of 2133 women (serum triglyceride <400 mg/dL) were included in the study of this item, which was calculated using the Friedewald equation.

[b] A total of 2073 women underwent this examination at the option of the individual subjects.

* $P < .05$.

† $P < .0001$.

currently receiving medication for diabetes mellitus or coronary heart disease (Table 3).

3.4. Age-adjusted odds ratios of other metabolic risk factors and sedentary history in women with reference to those without metabolic syndrome when substituting an anthropometric index for the definition of metabolic syndrome

In women, the age-adjusted odds ratios of other metabolic risk factors and sedentary history were all significantly higher in those with metabolic syndrome than in those without metabolic syndrome, irrespective of the anthropometric index used for the definition, even excluding those currently receiving medication for diabetes mellitus or coronary heart disease (Table 4).

4. Discussion

Although the definition of *metabolic syndrome* according to AHA/NHLBI is a term for a constellation of risk factors that increase the risk of the development of both atherosclerotic cardiovascular diseases and type 2 diabetes mellitus [2], there is increasing evidence that fatty liver, elevated liver enzymes, hyperuricemia, etc, may also be associated with the metabolic syndrome [31-33]. However, the anthropometric indices from most of the above data were derived from Adult Treatment Panel III [1].

Our data show that significantly greater risk of high LDL cholesterol, fatty liver, high γ-glutamyltransferase, and sedentary history exists simultaneously in both men and women with metabolic syndrome as defined by AHA/

Table 3
Age-adjusted odds ratios (95% confidence interval) of other metabolic risk factors and sedentary history in men with metabolic syndrome, with reference to those without metabolic syndrome when substituting an anthropometric index for the definition of metabolic syndrome

Anthropometric index	JASSO [4]	AHA/NHLBI for Asian Americans [2]	AHA/NHLBI for non–Asian Americans [2]	Our proposal [24]
	W ≥85 cm	W ≥90 cm	W ≥102 cm	WHtR ≥0.5
High LDL cholesterol	1.29 (1.14-1.45)†	1.35 (1.18-1.52)†	1.26 (1.08-1.48)*	1.33 (1.18-1.49)†
	1.28 (1.14-1.44)†	1.33 (1.17-1.52)†	1.27 (1.08-1.49)*	1.32 (1.17-1.49)†
Hyperuricemia	2.51 (2.20-2.87)†	2.57 (2.20-2.90)†	2.36 (2.01-2.77)†	2.60 (2.29-2.97)†
	2.51 (2.20-2.87)†	2.54 (2.21-2.92)†	2.38 (2.02-2.81)†	2.62 (2.29-2.99)†
High γ-glutamyltransferase	2.81 (2.41-3.27)†	2.83 (2.41-3.31)†	2.54 (2.11-3.03)†	3.02 (2.59-3.52)†
	2.84 (2.43-3.32)†	2.89 (2.46-3.40)†	2.58 (2.14-3.10)†	3.10 (2.65-3.62)†
Fatty liver	4.42 (3.92-4.98)†	4.87 (4.23-5.54)†	4.43 (3.80-5.16)†	4.65 (4.13-5.24)†
	4.39 (3.89-4.96)†	4.83 (4.24-5.51)†	4.37 (3.74-5.10)†	4.62 (4.09-4.98)†
Sedentary history	1.40 (1.24-1.59)†	1.50 (1.31-1.73)†	1.37 (1.17-1.63)*	1.43 (1.26-5.21)†
	1.46 (1.28-1.65)†	1.57 (1.36-1.81)†	1.45 (1.22-1.73)†	1.48 (1.30-1.68)†

Underlined entries: excluding those currently receiving medication for diabetes mellitus or coronary heart disease.

* $P < .05$.

† $P < .0001$.

Table 4
Age-adjusted odds ratios (95% confidence interval) of other metabolic risk factors and sedentary history in women with metabolic syndrome, with reference to those without metabolic syndrome by substituting an anthropometric index for the definition of metabolic syndrome

Anthropometric index	JASSO [4]	AHA/NHLBI for Asian Americans [2]	AHA/NHLBI for non-Asian Americans [2]	Our proposal [24]
	W ≥90 cm	W ≥80 cm	W ≥88 cm	WHtR ≥0.5
High LDL cholesterol	2.44 (1.68-3.56)†	2.06 (1.55-2.73)†	2.63 (1.86-3.73)†	2.17 (1.66-2.84)†
	2.37 (1.63-3.48)†	2.09 (1.57-2.79)†	2.57 (1.81-3.67)†	2.20 (1.68-2.89)†
Hyperuricemia	7.20 (2.59-18.60)†	4.56 (1.71-11.67)*	6.21 (2.24-15.97)*	3.88 (1.46-9.94)*
	7.27 (2.61-18.80)†	4.60 (1.72-11.78)*	6.25 (2.25-16.08)*	3.91 (1.46-10.00)*
High γ-glutamyltransferase	3.07 (1.29-6.48)*	3.43 (1.72-6.53)*	4.05 (1.91-8.01)*	2.92 (1.46-5.56)*
	3.21 (1.35-6.81)*	3.61 (1.80-6.91)*	4.24 (1.99-8.42)†	3.07 (1.53-5.87)*
Fatty liver	11.67 (8.01-17.12)†	10.32 (7.61-14.04)†	12.27 (8.58-17.66)†	9.43 (7.01-12.71)†
	11.80 (8.08-17.35)†	10.35 (7.60-14.13)†	12.45 (8.68-17.96)†	9.51 (7.05-12.85)†
Sedentary history	1.60 (1.08-2.43)*	1.44 (1.07-1.96)*	1.72 (1.19-2.56)*	1.43 (1.08-1.91)*
	1.63 (1.09-2.48)*	1.43 (1.06-1.95)*	1.75 (1.20-2.61)*	1.42 (1.07-1.90)*

Underlined entries: excluding those currently receiving medication for diabetes mellitus or coronary heart disease.
* $P < .05$.
† $P < .0001$.

NHLBI by substituting various proposed anthropometric indices of central fat distribution, including WHtR.

We are not surprised by the much lower rate of "currently receiving medication" in this study than the estimated prevalence of DM in Japan. The reasons are as follows: (1) mild cases were symptomless, and those affected might not visit diabetic clinics; (2) some mild to moderate cases might choose treatment by diet and exercise rather than medication, even if they visit diabetic clinics; (3) the subjects who received the health examinations might have been more highly motivated in health matters and, as a result, might have lower prevalence of DM than those who do not receive health examination or the estimated prevalence of DM in Japan; and (4) individuals with moderate to marked hyperglycemia might seek follow-up treatment at diabetic clinics rather than at the institutions performing health examinations.

Reaven [34] proposed that insulin resistance plays a causal role in metabolic syndrome; however, the cause of this syndrome remains obscure [2]. Because overnutrition and/or overconsumption of alcohol contributes to lifestyle-related disorders, it is likely that high LDL cholesterol, hyperuricemia, high γ-glutamyltransferase, and fatty liver may also coexist in subjects with metabolic syndrome. It has been also reported that a sedentary lifestyle is associated with abdominal fat distribution, clustering of coronary risk factors, and metabolic syndrome [2,35,36].

High LDL cholesterol is an important factor for atherosclerotic heart disease; and hyperuricemia not only may cause gouty arthritis and chronic renal disease [37], but also may cause coronary heart disease [38]. γ-Glutamyl-transferase is mainly seen as an indicator of liver function and alcoholic consumption. However, this enzyme may also play a role in the pathogenesis of atherosclerosis and cardiovascular disease mortality [39,40]. Fatty liver, whether alcoholic or nonalcoholic, may be a factor in hepatitis, cirrhosis, and hepatoma [41,42].

Thus, in addition to the risk factors included in the present definition, metabolic syndrome may involve many risk factors that may cause serious disorders of multiple organs. For this reason, attention should also be paid to other risk factors in subjects with metabolic syndrome, irrespective of different definitions. Further study is needed to clarify the most appropriate definition of metabolic syndrome so as to include the spectrum of risk factors that best represents the future risk of cardiovascular and other diseases, so that early lifestyle modification and/or treatment can be started [43].

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